UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/419,545	10/18/1999	AYUB DARJI	29473/10277	1400

7590 03/29/2002

MARSHALL O'TOOLE GERSTEIN MURRAY
AND BORUN
6300 SEARS TOWER
233 SOUTH WACKER DRIVE
CHICAGO, IL 606066402

EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	17

DATE MAILED: 03/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/419,545	Darji et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 3, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-10* ~~is~~/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-10* ~~is~~/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☒ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5 & 10.*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Preliminary Amendment

1) Acknowledgment is made of Applicants' preliminary amendment filed 01/24/01 (paper no. 8). With this, Applicants have amended the specification.

Election

2) Acknowledgment is made of Applicants' invention election filed 06/11/01 (paper no. 13) and species election filed 01/03/02 (paper no. 16). Applicants elect, without traverse, invention I, claims 1-10, in response to the restriction requirement mailed 03/09/01 (paper no. 11). Applicants elect, with traverse, the first species, i.e., *E. coli* beta-galactosidase (LacZ gene) recited in claim 9, in response to the species election requirement mailed 08/16/01 (paper no. 14). Applicants submit that three species do not exceed a reasonable number of species and therefore a search for all the species would not be unduly burdensome. Applicants request that all the three gene species be examined. Upon reconsideration, the three heterologous gene species recited in claim 9 have been rejoined and examined.

Status of Claims

3) Claims 11-16 have been canceled via the paper filed 06/11/01.

The elected claims 1-10 are under examination. An Action on the Merits for these claims is issued in the instant Office Action (paper no. 17).

Priority

4) The instant application is a continuation-in-part of the PCT application, PCT/EP97/06933, filed 12/11/97, which claims foreign priority to the application, 97 106503.2, filed 04/18/97 in Federal Republic of Germany. It is noted that a certified copy of the priority document has **not** been submitted in this case.

Drawings

5) The drawings are objected to under 37 CFR 1.84 because of the reasons set forth by the Draftsperson in the attached Form PTO 948 (paper no. 17). Correction is required. Applicants are asked to note the changes effected 03 May 2001, particularly the changes to the 'Timing of Corrections':

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR.1.85; 1097 O.G. 36

New formal drawings must be filed with the changes incorporated therein. The art unit number, application number (including series code) and number of drawing sheets should be written on the reverse side of the drawings. Applicant may delay filing of the new drawings until receipt of the "Notice of Allowability" (PTOL-37 or PTO-37). If delayed, the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability" to avoid extension of time fees. Extensions of time may be obtained under the provisions of 37 C.F.R 1.136(a) for filing the corrected drawings (but not for payment of the issue fee). The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the three month shortened statutory period set in the "Notice of Allowability" (PTO-37). Within that three month period, two weeks should be allowed for review of the new drawings by the Office. If a correction is determined to be unacceptable by the Office, Applicant must arrange to have an acceptable correction re-submitted within the original three month period to avoid the necessity of obtaining an extension of time with extension fees. Therefore, applicant should file corrected drawings as soon as possible.

Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

Sequence Listing

6) Acknowledgment is made of Applicants' raw sequence listing which has been entered on 02/05/01 (paper no. 9).

Information Disclosure Statements

7) Acknowledgment is made of Applicants' Information Disclosure Statements filed 03/10/00 and 03/28/00 (paper no. 5 and 10). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 17).

Abstract

8) The abstract of the disclosure is objected to because it is presented in more than one paragraph and it exceeds the number of permitted words. Correction is required. See MPEP § 608.01(b).

Specification - Informalities

9) The specification is objected to for the following reasons:

(i) The instant application is informal in the format or arrangement of the specification. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the Applicants' use.

Content of Specification

(a) Title of the Invention: See 37 C.F.R 1.72(a). The title of the invention should be placed at the top of the first page of the specification. It should be brief but technically accurate and descriptive, preferably from two to seven words.

(b) Cross-References to Related Applications: See 37 C.F.R 1.78 and M.P.E.P § 201.11.

(c) Statement Regarding Federally Sponsored Research and Development: See M.P.E.P § 310.

(d) Reference to a "Microfiche Appendix": See 37 C.F.R 1.96(c) and M.P.E.P § 608.05. The total number of microfiche and the total number frames should be specified.

(e) Background of the Invention: The specification should set forth the Background

of the Invention in two parts:

(1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the applicable U.S. patent classification definitions of the subject matter of the claimed invention. This item may also be titled "Technical Field."

(2) Description of the Related Art: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art."

(f) Brief Summary of the Invention: A brief summary or general statement of the invention as set forth in 37 C.F.R 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in the Background of the Invention). In chemical cases it should point out in general terms the utility of the invention. If possible, the nature and gist of the invention or the inventive concept should be set forth. Objects of the invention should be treated briefly and only to the extent that they contribute to an understanding of the invention.

(g) Brief Description of the Several Views of the Drawing(s): A reference to and brief description of the drawing(s) as set forth in 37 C.F.R 1.74.

(h) Detailed Description of the Invention: A description of the preferred embodiment(s) of the invention as required in 37 C.F.R 1.71. The description should be as short and specific as is necessary to describe the invention adequately and accurately. This item may also be titled "Best Mode for Carrying Out the Invention." Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in

detail. However, where particularly complicated subject matter is involved or where the elements, compounds, or processes may not be commonly or widely known in the field, the specification should refer to another patent or readily available publication which adequately describes the subject matter.

(i) Claim or Claims: See 37 C.F.R 1.75 and M.P.E.P § 608.01(m). The claim or claims must commence on separate sheet. (37 C.F.R 1.52(b)). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. There may be plural indentations to further segregate subcombinations or related steps.

(j) Abstract of the Disclosure: A brief narrative of the disclosure as a whole in a single paragraph of 250 words or less on a separate sheet following the claims.

(k) Drawings: See 37 C.F.R 1.81, 1.83-1.85, and M.P.E.P § 608.02.

(l) Sequence Listing: See 37 C.F.R 1.821-1.825.

The instant specification is further objected to because of the reasons given below:

(ii) The name of a bacterial species in the instant specification is misspelled. For example, see "*typhii*" on page 3, third full paragraph and claims 4 and 5. Certain terms are improperly spaced. For example, see page 3, line 13: "listerio lysin". The art-recognized recitation is --listeriolysin–. See the abstract of Mengaud *et al.* (*Infect. Immun.* 56: 766-772, 1988 - Applicants' IDS).

(iii) Figures 1, 2, 4, 5 and 8 are incorrectly identified. The different panels in these Figures should be individually renumbered. For example, Figures 1and 2 should be labeled or numbered as Figure 1A, 1B, 1C, 1D, 1E and 1F and Figure 2A, 2B, 2C, 2D, 2E and 2F. Analogous criticism applies to Figure 4, 5 and 8. Individual Figure descriptions in the specification on pages 15-18 should be amended to read Figures 1A to 1F and so on. The recitation "Legends to Figures" on page 15 should be replaced with --Brief Description of the Drawings--. All references to these Figures in the specification should be amended to reflect these changes in numbering.

(iv) The use of the trademark in the instant specification has been noted in this application. For example, see page 22, middle paragraph: "Tween 20"; and page 23, last

paragraph: "Triton X-100". The recitation should be capitalized wherever it appears and be accompanied by the generic terminology. Each letter of the trademark must be capitalized. See M.P.E.P 608.01(V) and Appendix I. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification to make similar corrections to the trademarks, wherever such recitations appear.

(v) The incorporation of essential material by reference to a foreign application or foreign patent or to a publication inserted in the specification in improper (see page24, last paragraph). Applicants are required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the Applicant, or Applicant's attorney or agent, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157; *In re Hawkins*, 486 F.2d 579, 179 USPQ 163; *In re Hawkins*, 486 F.2d 577, 179 USPQ 167.

(vi) The instant specification contains the abbreviated recitation "CMV" (see for example, page 5, lines 3, 4, 8 and 10). It is unclear what does this abbreviation stand for.

(vii) The names of the bacterial species in the instant specification are not italicized. For example, see page 2, lines 13-21 and 30-31; page 3, line 8, and page 3, lines 23-26. To be consistent with the practice in the art, it is suggested that the names of the bacterial species be italicized. It is suggested that Applicant review the whole specification and make similar corrections wherever necessary.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

10) Claim 3 is rejected under 35 U.S.C § 112, first paragraph, as failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description, e.g., sequenced; or (3) deposited.

Instant claims are directed to attenuated *Salmonella* strains comprising a eukaryotic

expression vector, including the specific *Salmonella* strains recited in claim 3: *Salmonella typhimurium* strains SL 7207, LT2 and aroAA544 (ATCC accession no. 33275). It is apparent that the recited strains are required to practice the claimed invention. As a required element, the strains must be known and readily available to the public, or obtainable by a reproducible method set forth in the specification, or otherwise be readily available to the public. If not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the recited strain.

From a review of the instant specification, it appears that the above-identified strains of *Salmonellae* are not deposited in a recognized depository. The strains do not appear to be readily available to the public and it is unclear if the strains can be reproducibly isolated without undue experimentation. Without a publicly available deposit of the strains, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Deposit of the claimed *Salmonella* strains would satisfy the requirements of 35 U.S.C. § 112, first paragraph.

If a deposit has already been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by Applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository, is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each state. The statement should identify the deposited strain(s) by its depository accession number, establish that the deposited strain(s) is the same as the one described in the specification, and establish that the deposited strain(s) was in the Applicants' possession at the time of filing. As a means of satisfying the necessary criteria of the deposit rules and to show that the deposited strains(s) is the same as the one(s) deposited, Applicants may submit a copy of the contract or a notice of acceptance of the strain(s) by the depository.

Further, the specification should be amended to include complete deposit information for

the *Salmonella* strains, including full address of the depository and the date of deposition. Additionally, Applicants are requested to amend the specification and the claim(s) with the proper information regarding the depository number and provide evidence to support the insertion for the depository number. The recitation of a laboratory designation does not clearly define the claimed *Salmonella* strains. Amending the claim to include the cell line deposit number following the laboratory designation is suggested for clarity.

Applicants' attention is directed to *In re Lundack*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 C.F.R § 1.801-1.809 for further information concerning deposit practice.

11) Claims 1-10 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for an attenuated *Salmonella* strain comprising a eukaryotic expression vector for expressing a heterologous gene wherein said vector comprises said gene within an open reading frame and expresses an *E. coli* beta-galactosidase, *Listeria monocytogenes* listeriolysin, or *Listeria monocytogenes* ActA protein, does not reasonably provide enablement for such an attenuated *Salmonella* strain wherein an autologous gene, or a fragment of a heterologous or autologous gene is expressed and wherein the strain is suitable for vaccination of vertebrates, as claimed currently. Furthermore, other than the specific listeriolysin variant and ActA variant described in the first paragraph on page 5 of the specification, the instant disclosure does not reasonably provide enablement for an attenuated *Salmonella* vaccine strain expressing 'any' truncated variant of a *Listeria monocytogenes* listeriolysin or 'any' truncated variant of a *Listeria monocytogenes* ActA protein, as claimed broadly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;

The presence or absence of working examples of the invention;
The nature of the invention;
The state of the art;

- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to an attenuated *Salmonella* vaccine strain. The breadth of claims 1-6, 9 and 10 encompasses an attenuated *Salmonella* strain, including *S. typhimurium* or *S. typhi,* that is suitable for vaccination, which strain comprises a eukaryotic expression vector for the expression of a heterologous or autologous gene or a gene fragment thereof. While the attenuated *Salmonella* strain encompassed in the scope of claims 7 and 8 is required to encode or express a polypeptide, an immunogenic protein or a protective antigen, the *Salmonella* strain claimed in claims 1-6, 9 and 10 is required to comprise said gene or gene fragment, but is not required to express the gene or gene fragment. The instant specification does not identify the structural compositions of a "fragment" of a heterologous and an autologous gene. It should be noted that a single nucleotide base constitutes a gene fragment and is encompassed in the fragment recited, for example, in claim 1. However, a *Salmonella* strain comprising such a fragment is unlikely to serve as a "suitable" vaccine for vertebrates. There is no description in the instant specification that guides one of skill in the art as to which fragment from which part of a heterologous or autologous gene (i.e., central or terminal parts, or both) could be chosen for inclusion in the claimed *Salmonella* strain such that the strain expresses a functional protein or polypeptide product and serves as a vaccine suitable for use in vertebrates.

The purpose of the instant invention is to provide an attenuated *Salmonella* strain that serves as an effective vaccine in vertebrates. With regard to claim 8, there is lack of disclosure as to the precise disease (infectious or non-infectious) or the clinical condition, which the recited antigen is allegedly "protective" against. There is no evidence that an attenuated *Salmonella* strain expressing a generic "polypeptide", or a generic "immunogenic protein", as claimed in claims 7 and 8, would serve as a suitable vaccine in vertebrates. It is well known in the art that not all immunogenic bacterial proteins are protective against a disease. In fact, the instant specification demonstrates that a *S. typhimurium aroA* strain carrying a eukaryotic expression plasmid, pCMVactA, encoding amino acids 31-613 of the ActA protein of *Listeria*

monocytogenes, failed to induce a protective immune response (see paragraph bridging pages 16 and 17; and Figure 4). Therefore, such a strain would not be considered by those skilled in the art as a strain "suitable for vaccination of vertebrates" against listeriosis.

As recited currently in a broad sense in claim 9, a *Salmonella* strain expressing a myriad of truncated variants of listeriolysin or truncated variants of actA protein of *Listeria monocytogens*, are encompassed in the scope of the claim. However, the only truncated and non-hemolytic variant of listeriolysin that is enabled or shown to be expressed via the claimed *Salmonella* strain is a variant that consists of amino acids between positions 26-482. Similarly, the only truncated variant of ActA membrane protein that is enabled or shown to be expressed via the claimed *Salmonella* strain is a variant that consists of amino acids between positions 31-613 (see page 5). While the former strain expressing said listeriolysin variant was demonstrated to be a protective vaccine against challenge with *Listeria monocytogenes*, the latter strain expressing said ActA variant was shown to be a non-protective vaccine against challenge with *Listeria monocytogenes*. See Figure 4. Outside this scope, the specification does not enable a *Salmonella* strain that expresses a listeriolysin or ActA gene truncated in any other way wherein the truncated gene expresses a functional, i.e., immunogenic and/or protective, listeriolysin variant or ActA membrane protein variant, as claimed in a broad sense. Even the enabled truncated variant of ActA membrane protein when expressed via the claimed *Salmonella* strain did not prove to be a suitable (protective) vaccine for vertebrates against listeriosis (see Figure 4). This is critical, because the expression of a truncated bacterial polypeptide by truncating any of part the gene responsible for its expression such that it retains its three dimensional conformation and remains functionally and/or biologically active, is not a predictable event. Therefore, there is no certainty that any other randomly truncated variant of ActA, if expressed via the claimed *Salmonella* strain, would prove to be "suitable for vaccination of vertebrates".

Similarly, there is no certainty that if one produced any other truncated variants of listeriolysin other than that described on page 5, first paragraph, and expressed it via the attenuated *Salmonella* strain, such a strain would serve as an effective vaccine in vertebrates. There is no certainty that the resultant truncated listeriolysin variant would loose the haemolytic activity and retain the functional integrity or biological/immunogenic competence of the native

listeriolysin. The state of the art clearly shows that a mutation or genetic variation at any random position of a wild-type bacterial polypeptide, pneumolysin, which shows sequence homology with listeriolysin, does not always result in a modified pneumolysin polypeptide having an attenuated hemolytic activity. For example, Mengaud *et al.* (*Infect. Immun.* 56: 766-772, 1988 - Applicants' IDS) teach the existence of homologies between the ORF of listeriolysin and pneumolysin (see page 766). Feldman *et al.* (*Am. J. Respir. Cell Mol. Biol.* 5: 416-423, 1991) show that, while a Trp 433 > Phe modification results in a modified pneumolysin having a lowered haemolytic activity, a Tyr 384 > Phe modification results in a modified pneumolysin that had normal hemolytic activity (see page 417). Mitchell *et al.* (*Mol. Microbiol.* 5: 1883-1888, 1991) show that individual modifications of Trp 379 and Trp 397 to Phe, or of residues Tyr 384 and Asp 385 to Phe and Asn respectively, did not alter the cytolytic activities of resultant modified pneumolysins (see page 1885, left column). Similarly, Bowie *et al.* (*Science*, 247: 1306-1310, 1990) teach that while it is known that many amino acid variations or substitutions are possible in any given protein, the position within the protein's sequence where such amino acid variations or substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (see column 2 on page 1306). Clearly, the breadth of the instant claim is not commensurate in scope with the enabling disclosure and/or evidence and clearly, one skilled in the art cannot make and use the invention commensurate in scope with the claims without undue experimentation.

Although a microbial polypeptide or protein when expressed via an attenuated bacterial strain is expected by those skilled in the art to generally induce specific antibodies, the ability of a "truncated variant" of such a polypeptide to serve as an effective vaccine "suitable for vaccination of vertebrates" when similarly expressed, is not certain. The instant specification fails to teach how to express any other "truncated variant" of listeriolysin or ActA membrane protein such that the bacterial strain expressing the same is capable of serving as a vaccine "suitable for vaccination of vertebrates". The specification provides no guidance as to which specific amino acids may be truncated or varied without causing any detrimental effect to the

polypeptide which is to be expressed via the *Salmonella* strain meant for use as a vaccine in vertebrates. There is no disclosure in the instant specification with regard to which other amino acid variations, i.e., truncations, in listeriolysin or ActA membrane protein, would result in a ActA "variant" or a non-hemolytic listeriolysin "variant" that would be immunogenically and biologically functional as the native polypeptide. This is important because the art reflects unpredictability as to which amino acids in a specific polypeptide can be varied, i.e., replaced or added, without adversely affecting the functional properties of that specific polypeptide. While it is known in the art that truncation or variation in one or more amino acids is possible in a given bacterial polypeptide, the exact position within its amino acid sequence where truncations or variations can be made, with a reasonable expectation of success of retaining the polypeptide's functional integrity, is not certain. A random truncation affecting the epitopic amino acid positions that are critical, for example, to the three-dimensional conformational structure and specific binding or protective property of the protein, would result in a polypeptide that may be non-functional (i.e., non-immunogenic or non-protective) or not optimally immunogenic or protective as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites; multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool.

Thus, the art reflects that variations in critical residues at specific positions in an amino acid sequence could result in a polypeptide which may induce an antibody that may not recognize or bind to the native polypeptide of a microorganism. In the instant case, this is important because one of the purposes of the instant invention is to produce a *Salmonella* strain expressing a heterologous polypeptide or protein that is "suitable for vaccination of vertebrates" as recited in claim 1, or wherein the expressed polypeptide serves as a "protective antigen" as recited in claim 8.

In view of the recognized unpredictability of expressing a truncated bacterial polypeptide which retains its three dimensional structure and biologic, protective and/or immunogenic functions by truncating any part of its gene, Applicants' own evidence showing that the *Salmonella* strain expressing a specific truncated variant of the ActA membrane protein proved to be a non-protective vaccine against challenge with *Listeria monocytogenes*, the art-demonstrated unpredictability in determining amino acid variations that result in non-hemolytic variants of listeriolysin, the lack of disclosure and working examples enabling the full scope, the quantity of experimentation necessary and the breadth of the claims, undue experimentation would have been required by one of ordinary skill in the art to reproducibly practice the full scope of the invention as claimed. One of ordinary skill in the art would not be able to make and use the claimed *Salmonella* strain, for example, as a vaccine, without undue experimentation, because there is no disclosure as to what positions and what specific amino acid residues are embraced by the "fragment" recited in the claims. The production and use of the claimed *Salmonella* strain that is capable of serving as a suitable vaccine for vertebrates is well outside the realm of routine experimentation. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

12) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

13) Claims 1-10 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) In claims 1 and 7, it is unclear what is encompassed in the recitation "fragment", or what characteristics and/or length a gene should have in order to qualify as a fragment. Does a single or double nucleotide base(s) of a gene qualify as a fragment?

(b) Claim 6 is vague in the recitation "facultatively" (see part c of the claim), because it is unclear what is encompassed in this recitation, or what purpose does it serve in the claim.

(c) In claim 9, it is unclear what is encompassed in the recitation "variant", or what

structural and/or functional characteristics the recited hly or actA gene should have in order to qualify as a "variant". It is unclear in what way the gene is varied: structurally or genetically, or biologically and functionally, in order to qualify as a 'variant'.

(d) Claim 8 is vague in the recitation: "protective" antigen (see line 2). Claim 8 depends from claim 7, which recites a polypeptide. In claim 8, it is unclear what the recited antigen is "protective" against: an infectious disease, a non-infectious illness or any other clinical or non-clinical condition.

(e) Claim 6 is vague and indefinite in the abbreviated recitation "CMV", because it is unclear what does it stand for. It is suggested that the abbreviation be recited as a full terminology at first occurrence in the base claim, with its abbreviated recitation retained in parentheses.

(f) Claims 2-9, which depend directly or indirectly from claim 1, are also rejected under 35 U.S.C. § 112, second paragraph, because of the indefiniteness or vagueness in the base claim(s) identified above.

Objection(s)

14) Claims 1, 4-6 and 9 are objected to for the following reasons:

(a) In the last line of claim 1, for clarity, it is suggested that Applicants replace the recitation "a vaccination" with --vaccination--.

(b) Claims 4 and 5 are objected to for the incorrectly spelled recitations: "*S. typhii*" . To obviate the objection, it is suggested that Applicants replace the recitation with --*S. typhi*–.

(c) To be consistent with the practice in the art, in claims 1 and 6, it is suggested that Applicants replace the recitation "eucaryotic" with --eukaryotic--.

(d) Claim 9 is objected to for the incorrectly spaced recitation "listerio lysin" (see line 3). To be consistent with the practice used in the art, it is suggested that Applicants replace the recitation with --listeriolysin–.

Remarks

15) Claims 1-10 stand rejected.

16) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile

transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9306.

17) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

S. DEVI, PH.D.
PRIMARY EXAMINER

March 2002